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Overview of the clinical implementation of a study exploring social withdrawal in patients with schizophrenia and Alzheimer's disease

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ABSTRACT

Trans-diagnostic, domain- or symptom-focused approaches have been heralded as advancing psychiatric research, but relatively few clinical research programmes have been undertaken to leverage their potential. In this manuscript we describe the approach and protocol for an exploratory study, PRISM (Psychiatric Ratings using Intermediate Stratified Markers), that will be conducted to explore the biomarkers in schizophrenia (SZ) and Alzheimer's Disease (AD) that may be related to a common symptom, social withdrawal. Patient participants (N = 72 SZ and N = 72 AD study completers), will complete a series of fMRI, EEG, and behavioural paradigms, as well as contributing blood-derived (e.g. epigenetic) and smartphone data related to social behaviour. Self- as well as caregiver- and researcher-reported assessments will be provided to characterise social withdrawal. Normative data will also be collected from a group of healthy controls (N = 48 study completers), half of whom will be matched in terms of age and gender distribution to the SZ and AD group, respectively. Thus we will explore both differentiation and cross-diagnostic overlap in the biomarkers associated with different levels of social withdrawal in SZ and AD. In this way we aim to provide a deeper understanding of the biological underpinnings of symptomatology common to both disorders, and provide insights into novel treatment targets and future drug development approaches.

1. Background

There is a growing acknowledgement that psychiatric and neurodegenerative disorders overlap much more than previously thought, and indeed, that they may better be described as domains of trans-diagnostic traits rather than separable categories (Insel and Cuthbert, 2015; Kas et al., 2007). The ability to precisely link clinical symptoms or characteristics to underlying neurobiology could facilitate the development of better treatments and treatment approaches, including patient stratification. The value of trans-diagnosic approaches has been further emphasized by the conclusions from the recent 'EU Roadmap for Mental Health in Europe' (ROAMER) project, involving over 1000 scientists, patients, families and professional groups from across Europe; the second priority for mental health research in Europe was a focus on causal mechanisms of mental disorders, identifying factors underlying co- and multi-morbidity, and extending research on single disorders to examine

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease assessment scale-cognitive; ASL, arterial spin labelling; CNS, central nervous system; CPT, continuous performance test; DSM, diagnostic and statistical manual of mental disorders; DSST, digit symbol substitution test; DTI, diffusion tensor imaging; EEfRT, effort expenditure for rewards task; EEG, electroencephalography; ESRS, extrapyramidal symptom rating scale; FEP, facial expression processing task; FERT, facial expression recognition task; FLAIR, fluid attenuation inversion recovery; MDD, major depressive disorder; MINI, mini-international neuropsychiatric interview; MMN, mismatch negativity; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; MSID, monetary and social incentive delay task; PANAS, positive and negative affect scale; PANSS, positive and negative syndrome scale; QIDS-SR16, quick inventory of depressive symptomatology, self-rated, 16 item version; STAI, state-trait anxiety inventory; SZ, schizophrenia; WHODAS, World Health Organisation disability assessment schedule

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common psychopathology across disorders (Wykes et al., 2015).

The PRISM consortium (Psychiatric Ratings using Intermediate Stratified Markers) aims to conduct a cross-disorder clinical study involving initially two brain disorders, schizophrenia (SZ) and Alzheimer's disease (AD), with a focus on a common clinical feature: social withdrawal. In a second phase of the project we aim to include participants with other diagnoses (e.g. major depressive disorder (MDD), a disorder also associated with social withdrawal). Withdrawal from friends, family, and colleagues, is one of the symptoms that is particularly burdensome for relatives of those affected by SZ or AD, and interestingly is one of the earliest signs of disease in both groups of patients (Reichman and Negron, 2001; Nelis et al., 2011; Cullen et al., 2011).

We selected these disorders because they share not only social withdrawal, but also some cognitive deficits (Cohen et al., 2013; Martinez-Aran and Vieta, 2015; Weintraub et al., 2012), which are known to contribute to interpersonal behaviour (Bowie et al., 2008). Deficits in working memory and attention found in drug-naïve and first episode patients with SZ (Fatouros-Bergman et al., 2014; Mesholam-Gately et al., 2009) are also found in the very early stages of AD, including in patients with Mild Cognitive Impairment (Weintraub et al., 2012). Interestingly these deficits are also among the most recognized cognitive impairments seen in patients with MDD (McIntyre et al., 2013). Further, sensory processing - a term that refers to the way the nervous system receives messages from the senses and turns them into appropriate motor and behavioural responses - is found to be impaired in all three disorders at the earliest stage of disease (McIntyre et al., 2013; Mesholam-Gately et al., 2009; Weintraub et al., 2012) (see also Kas et al. (in press)).

Cognitive deficits within domains including working memory, attention, and sensory processing are thus similar across diagnostic groups and may represent trans-diagnostic processing domains related to social withdrawal. In fact, some data suggest that interpersonal behaviour could be predicted by processing speed, attention and working memory, together with executive functions and depressive and negative symptoms, with social competence as a mediating factor (Bowie et al., 2008). A number of studies have shown that loneliness, itself likely to be linked (although not parsimonious) with social withdrawal, is a risk factor for cognitive decline (Tilvis et al., 2004; Wilson et al., 2007; Gow et al., 2007) (see also Porcelli et al., van der Wee et al., this issue). Loneliness has also been associated with amyloid burden, itself one of the most promising biomarkers of AD (Donovan et al., 2016), and has been linked with psychotic sympoms in a recent meta-analysis (Michalska da Rocha et al., 2018). In assessing the cognitive abilities of almost 500 birth-cohort individuals at age 11 and age 79, Gow et al. (2007) found that loneliness was the only social characteristic that significantly predicted cognitive ability at age 79 after controlling for factors including sex, years of education, social class, and early-life cognitive ability (at age 11). The link between social withdrawal and fundamental aspects of cognition have also been established in animal studies (Schrijver et al., 2004).

A deep and combined cross-disorder investigation of these domains may lead to significant advances in the understanding of the biological underpinning of these impairments, paving the way for the development of novel treatments targeted at both social withdrawal and cognitive deficits in SZ, AD, and MDD. However, we know of no previous studies that directly compare SZ, AD and MDD and contrast data from these patient groups within a single study and using shared experimental tools, despite the clinical and cognitive/neuroiological commonalities. Thus, even though there is increasing awareness of cross-disorder overlap in symptomatology and pathophysiology between psychiatric disorders, and even between psychiatric and neurological disorders, examples of true cross-diagnostic approaches in the conduct of research are limited.

Here, we describe the protocol of the clinical PRISM (Psychiatric Ratings using Intermediate Stratified Markers) study, that aims to explore the biological underpinnings of social withdrawal in SZ and AD. Our conceptual and methodological approach draws heavily on the Research Domain Criteria (RDoC) framework proposed by the National Institute of Mental Health (NIMH) (Insel et al., 2010), and the adaptations and recommendations formulated in the ROAMER initiative (Wykes et al., 2015) (see also Kas et al, in this issue). What this encapsulates is an approach that aims to identify cross-diagnostic *behavioural* and *neural phenotypes*. This phenotype-driven approach is different from the predominant clinical research and treatment approaches, in which patients with neuropsychiatric disorders are grouped into non-overlapping diagnostic categories, e.g. 'schizophrenia' and 'Alzheimer's Disease', and are then investigated or treated according to their categorical diagnosis. While these diagnostic categories are sufficient to provide the basis for general clinical management, they might be 'artificial' distinctions that do not describe the underlying neurobiology that gives rise to individual symptoms or other relevant aspects of the clinical profile.

The overarching objectives of the PRISM clinical study are:

(1) To establish whether a set of quantifiable biological parameters can cluster and differentiate SZ and AD patients characterised by different levels of social withdrawal, and,
(2) To identify and validate biological substrates and cognitive processes for social withdrawal in SZ and AD, through the use of quantitative technologies.

In order to address these objectives, SZ and AD patients with different levels of social withdrawal, as well as healthy control participants, will be selected and compared on an array of cognitive, attentional, and sensory processing assays. As age has well established effects on many aspects of neural and cognitive function, and the age of SZ and AD patients will differ significantly (with AD patients being older), it is essential to control for the effects of age on performance of the study tasks. By collecting age-matched healthy control data we will be better able to establish which effects are associated with disease or symptomology, rather than simply with the normal effects of aging.

Participants will complete (f)MRI and EEG assessments, as well behavioural tasks and questionnaires, selected following rigorous review of the literature by expert PRISM consortium members to probe the neural and behavioural correlates of social withdrawal, and its link with cognition (see van der Wee et al., Gilmour et al., Porcelli et al., and Danjou et al., in this issue). ASL (Arterial Spin Labelling) scan data will be collected to measure blood perfusion of the brain, and DTI (Diffusion Tensor Imaging) and FLAIR (FLuid Attenuation Inversion Recovery) MRI sequences will provide data about neural white matter, including white matter integrity and hyperintensities. As measures for social withdrawal are proxies that differ between cohorts, a single objective measure of social withdrawal will also be obtained from a smartphone application (BEHAPP, www.behapp.org; see also below).

The nature of this study, aimed at achieving deep phenotyping across a number of domains, requires many assessments. However, it is also constrained by cost and time pressures. Implementing the number, breath and in some cases the complexity of the tasks in the two patient populations - in which cognitive process and stamina may be compromised - also has its challenges. Recognising these issues, we have divided assessments over a number of days with the flexibility to allow assessments scheduled for a particularly day to be carried over to the next assessment day. Site staff can also, at their discretion, either not initiate or terminate an assessment if in their opinion the participant is unable to complete an assessment (e.g. if the participant is fatigued, cannot comprehend the instructions for a task, or cannot physically complete a task). We will continuously monitor feasibility of the study and the quality of our collected data. This could potentially result in some minor adaptations to the research protocol if problems are experienced, which will be informative for future researchers in the field of cross-disorder phenotyping.

2. Methods and study design

2.1. Study design

The study comprises an exploratory study of three groups: 1) patients with probable AD; 2) patients with SZ; and 3) a healthy control group, with half approximately matched in age distribution and gender proportion to the SZ group, and the other half to the AD group.

The study is conducted at three research sites in the Netherlands (University Medical center Utrecht, VU University Medical center Amsterdam and Leiden University Medical Center), and two research sites in Spain (both located in Madrid: Hospital General Universitario Gregorio Marañón, and Hospital Universitario de La Princesa). Each of the Dutch sites will conduct scanning at a respective MRI centre (UMC Utrecht, Spinoza imaging center in Amsterdam, and Leiden UMC) whilst for Spain, all scanning will be conducted in the same common MRI centre (Ruber International Hospital), leading to a total of 4 different MRI sites. We aim to recruit roughly the same number of participants for each group (SZ, AD or healthy controls) at each of the four MRI centres, allowing for the greatest control and statistical accounting of site effects.

2.2. Sample size

A maximum of 216 participants will be enrolled into the study, with the expectation that approximately 192 will complete the study. Approximately 160 patient participants (80 SZ, 80 AD) will be enrolled with the expectation that 144 (72 SZ, 72 AD) will complete the study. Approximately 56 healthy control participants, with age distributions and gender proportions similar to the (younger) SZ and (older) AD group, will be recruited, with the expectation that up to 48 healthy controls (24 younger, 24 older) will complete the study.

A formal sample size calculation is challenging because of the number and variety of outcome measures being explored and the scarcity of previous research on social withdrawal. This makes the estimation of effect sizes for this group comparison particularly difficult. However, based on previous fMRI group-level analyses for a version of the N-back task (highly similar to the task being used in the current study), we have conducted power calculations that suggest that 36 participants per group will be sufficient to detect significant differences between groups within our fMRI data, should they exist. Specifically, based on N-back fMRI data drawn from a 2-arm Randomised Controlled Trial (Smith et al., 2017), and using an anatomical left hippocampal Region of Interest (ROI), two power-calculations were performed using a 2-sample *t*-test design. Comparing drug vs. placebo, an effect size of 0.29 was estimated. Comparing remitted depression vs. control participants, an effect size of 0.76 was estimated. Assuming a similar Standard Deviation and a conservative effect size of 0.29 between, for example, the socially withdrawn AD and SZ groups in the present study, 30 participants in each group should be sufficient to detect group differences at 80% power. Therefore, our target sample size (N = 36) per group should be adequately powered to detect significant changes in brain activation at the standard statistical threshold ($p = 0.05$). These power calculations were performed with the software package fMRIpower (Mumford and Nichols, 2008).

2.3. Study population

Key inclusion and exclusion criteria for each participant group (SZ, probable AD, and HC) are described in Tables 1 and 2 below. Note that this does not represent a comprehensive account of all inclusion and exclusion criteria but, for brevity, captures what we judge to be the most essential demographic, medical, and procedural criteria.

Several of the inclusion and exclusion criteria merit further comment. Many of the inclusion and exclusion criteria serve the purpose of ruling out secondary sources of social withdrawal, such as depression (hence exclusion criterion based on the MINI and QIDS-SR16), extrapyramidal symptoms (hence the ESRS criterion among those patients receiving antipsychotic medication), psychosis (hence the criteria based on PANSS scores in the SZ group), or other concomitant medical disorders. Additionally, some of these criteria were adopted to follow the NIMH recommendations on clinical research into negative symptoms (Kirkpatrick et al., 2006). So, for example, exclusion of SZ patients demonstrating substantial drug-induced akinesia, depression, or other factors that are not part of the disease process itself, helps to avoid confounds associated with 'secondary' negative symptoms. Thus, the current study is designed to better explore the primary negative symptom of social withdrawal in SZ (i.e. as part of the disease process itself) and the relationship with cognitive dysfunction.

Although it did not form one of the strict inclusion or exclusion

Table 1
Inclusion and exclusion criteria applied to both the SZ (schizophrenia) and probable AD (Alzheimer's Disease) patient groups in the PRISM study (top), and healthy control volunteers (bottom). QIDS-SR16 = Quick inventory of Depressive Symptomatology, Self-Rated, 16 item version; MRI = Magnetic Resonance Imaging; MINI = Mini-International Neuropsychiatric Interview; MMSE = Mini-Mental State Examination; ESRS = Extrapyramidal Symptom Rating Scale; CNS = Central Nervous System; DSM = Diagnostic and Statistical Manual of Mental Disorders.

Key Inclusion criteria	Key Exclusion criteria
Inclusion and Exclusion Criteria applicable to **both SZ and probable AD patients**	
1 Not socially withdrawn due to external circumstances (e.g. lack of access to transport, e.g. rural location) or comorbid medical disorder or disability (e.g., hearing loss, lack of mobility, facial disfigurement).	1 Patients with a current DSM-IV diagnosis of MDD as assessed by the MINI, and with a QIDS-SR16 score of ≥16.
2 Right-handed or ambidexterous	2 Patients with or any other current primary psychiatric diagnosis requiring intervention other than AD or SZ that in the judgement of the investigator may affect the patient's ability to complete the study assessments.
	3 Chronic alcohol/drug abuse/dependence within previous 3 years.
	4 For patients currently taking antipsychotic medication, ≥4 on the global Parkinsonism item of the ESRS.
	5 Has any contraindications for MRI studies
	6 Has unstable comorbid somatic disorder with potential CNS sequelae, or, unstable dose regimen of medication that may affect CNS (i.e not stable for at least 8 weeks)
Inclusion and Exclusion Criteria applicable to healthy control volunteers	
1 Men and women, aged 18-45, inclusive (of similar age distribution and gender proportion to SZ group) or 50-80, inclusive (of similar age distribution and gender proportion to AD group)	1 Current, or history of, Axis-I psychiatric disorder as determined by the MINI, or neurological disease associated with cognitive impairment.
2 Right-handed or ambidextrous	2 > 5 on the QIDS-SR16 (indicative of mild or more severe depression)
3 Scores approximately average in the MMSE according to their age and years of education, as compared with normative data (no more than 1 mark below the average that would be expected).	3 Is currently, or has ever, required antidepressant or anxiolytic medication, including benzodiazepines
	4 Has within 6 weeks prior to the first assessment visit been prescribed a medication that may affect the CNS
	5 Has any contraindications for MRI studies

Table 2
PRISM clinical study inclusion and exclusion criteria specific to patients with schizophrenia and patients with probable Alzheimer's Disease (AD). MINI = Mini-International Neuropsychiatric Interview; MMSE = Mini-Mental State Examination; PANSS = Positive and Negative Syndrome Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders.

Patients with Schizophrenia		Probable Alzheimer's Disease patients	
Key Inclusion criteria	Key Exclusion criteria	Key Inclusion criteria	Key Exclusion criteria
1 Age 18 through 45 years. 2 DSM-IV diagnosis of SZ (confirmed on the MINI) with at least one confirmed psychotic episode, but maximum 10 years disease duration since diagnosis. 3 If the patient uses any antipsychotic, anticholinergic or antidepressant medication, dosage stable for at least 8 weeks.	1 A score of ≥22 on the 7-item PANSS positive symptom factor. The score of items for delusions, hallucinatory behaviour, suspiciousness and unusual thought content meet the following requirements: a No more than 2 of the above items have a score of 4. b All of the above items score less than 5. 2 In the clinician's judgment, patients who, for any reason, are considered to be a danger to themselves	1 Age 50 through 80 years 2 Probable AD, meeting the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria for probable AD. 3 MMSE score 20- 26.	1 Multiple strokes based on clinical judgement, as determined by history and/or imaging results where available.

criteria in the present study, younger and older healthy controls will, as far as possible, be recruited from similar geographical locations to those participants in the SZ and AD groups, respectively ("zip-code matching"). The intent is to address differences in objective social engagement data collected via the smartphone application, BEHAPP (e.g. proximity to number of Wi-Fi access points and Bluetooth devices) driven by residential location (e.g. urban vs. rural). Recruitment strategies for HC participants will target the relevant geographical regions.

2.4. Recruitment

Eligible patient participants will partly be identified via clinical programs affiliated with the participating study sites, during clinical assessments. Potentially eligible participants will be given a brief oral description of the study by their treating physician. If they are interested, the research team will explain the study in detail before obtaining informed consent.

SZ and AD participants will also be recruited from patient cohort registers available to the participating centres. The study will also be advertised through public engagement events and various media such as newspapers, posters, flyers, radio, mail-lists, and social media; it is expected that the majority of healthy control participants will be recruited via this latter route.

2.5. Procedure

Participants will attend the study centre on at least three assessment days. A simple schematic figure of the study design is shown in Fig. 1, below.

The first assessment day will include screening, collection of questionnaire measures, behavioural testing, a blood draw, and optional installation of a passive smartphone application (BEHAPP) on participants' phones. The second and third assessment days will each include an MRI and EEG neuroimaging session. For each participant, all assessment days will be as far as possible completed within 42 days from the 1st (screening) assessment visit, at which point collection of BEHAPP data will also be terminated. Some flexibility will be allowed on the study duration and the number of assessment visits required; for example, patient participants may opt to complete EEG and MRI sessions on different days. As far as possible the order of study events will be held constant across participants. All participants will be asked to complete a short set of follow-up questionnaires at the end of the study (+42 days), either online or by telephone.

Table 3 below summarizes the key behavioural, neural, and other assessments that are included in PRISM, together with the key constructs that are measured by each form of data or task.

We realize that our assessment protocol is extensive, and there is limited experience of any similarly burdensome protocol in both patient groups. Therefore, feasibility of our assessments will be closely monitored and amendments may take place if assessment burden is too high.

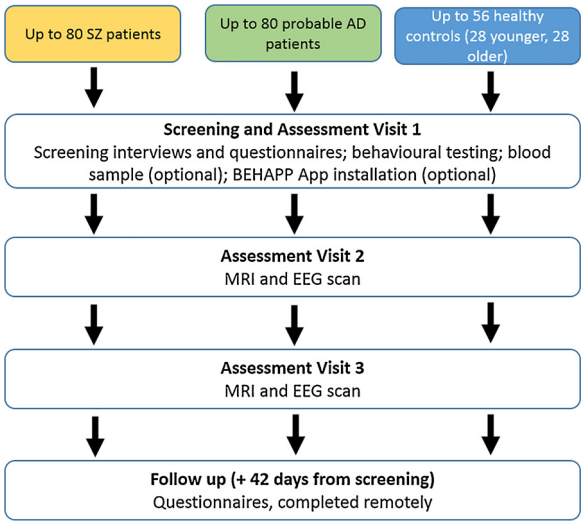

Fig. 1. Flow diagram of assessment days and main assessment components within the PRISM study schedule.

Patient participants (both SZ and probable AD) will be encouraged to attend all assessment visits with a "study partner", an individual who has regular contact with the participant. The aim is to improve the tolerability of the study for patient participants, and therefore foster better compliance with study procedures. In addition, study partners will be asked to rate the participant's degree of social withdrawal (see 'Characterisation of social withdrawal', below) and study partners of probable AD participants are additionally asked to complete one clinical assessment, the Neuropsychiatric Inventory (Cummings et al., 1994), to capture third-party information about the patient's symptom severity.

Overall trial management and monitoring will be the responsibility of the study sponsor (University Medical Centre, Utrecht). For more detailed descriptions of the tasks included, and the rationale for their inclusion, see van der Wee et al., Gilmour et al., Porcelli et al., and Danjou et al., in this issue. Note that not all recommended tasks were included in the final study protocol (e.g. the Attentional Network Task), due to constraints placed on the length of the assessment days to limit participant burden.

Table 3
Summary of key assessments that are included in PRISM, by modality, data type/task, constructs measured, and corresponding assessment visit.

Modality	Task Name / data	Key construct(s) or measures	Visit
MRI	T1 structural	Neural structure, morphology	2 & 3
MRI	Diffusion Tensor Imaging	White matter integrity, connectivity	3
MRI	T2 'FLAIR'	White matter hyperintensities	2
MRI	Arterial Spin Labelling	Cerebral blood perfusion	3
fMRI	N-back	Working memory	2
fMRI	Virtual Morris Water Maze	Spatial working memory	3
fMRI	Monetary and Social Incentive Delay task	Reward anticipation (social / monetary)	2
fMRI & EEG (separately)	Resting state	Brain activity when not performing explicit task; functional organisation	2
fMRI & EEG (separate)	Facial Emotion Processing task	Neural response to facial expression: social cognition/sensory processing	3 / 2
EEG	Auditory MMN (eyes open / eyes closed)	EEG oddball task: sensory processing	2 / 3
EEG	Auditory Steady State Response	EEG oddball task: sensory processing	2
Behavioural	Conners Continuous Performance Task	Attention, vigilance, impulsivity	1
Behavioural	Effort Expenditure for Rewards Task	Effort-based decision-making; anhedonia	1
Behavioural	Digit Symbol Substitution Task	General cognitive processing	1
Behavioural	Facial Emotion Recognition Task	Emotional bias	1
Behavioural	Hinting Task	Higher-order social cognition: mentalising/theory of mind	1
Passive smartphone monitoring	Passive smart-phone monitoring (BEHAPP)	E.g. proximity to Wi-Fi/Bluetooth devices; geolocation; social activity	Days 1-42
Blood	Blood sample analyses	Including epigenetics analysis	1

3. Scales, paradigm development, and systems implementation

3.1. Characterisation of social withdrawal

One of our aims in PRISM is to study the relationship between social withdrawal and cognition in AD and SZ, and search for both overlap and differentiation between the diagnostic cohorts based on this construct. We therefore require a study sample for which there is variation in social withdrawal exhibited by patient participants, and, good measures to quantify social behaviour. However, well-validated measures of social withdrawal do not yet exist. Indeed, improved tools to characterise social withdrawal are considered a valuable output of the present study. Taking a pragmatic approach, we selected items from the WHODAS 2.0 (WHODAS 2.0: World Health Organisation Disability Assessment Schedule 2.0) as our primary assessment of social withdrawal, given the extensive prior use of the WHODAS in both clinical (including SZ, AD and MDD) and in general populations; the open access availability of multiple language translations; and the short administration time, particularly for a single WHODAS domain. Items that were selected from the WHODAS 2.0 to characterise social withdrawal comprise of the following: dealing with people you know; maintaining a friendship; getting along with close people; making new friends; and joining in community activities.

Two other self-report scales directly related to social behaviour and perception will be collected: the Social Functioning Scale (Birchwood et al., 1990) and the De Jong Gierveld Loneliness and Affiliation Scale (de Jong-Gierveld, 1987). Importantly, to explore the validity of participant-reported responses we will additionally collect (where possible) caregiver- and also researcher-rated WHODAS scores. Data harvested from the BEHAPP app will also provide objective data related to social behaviour.

For more information about the selection of social withdrawal assessments in PRISM, see van der Wee et al., in this issue. We acknowledge our intention to examine the relationship between these measures of social withdrawal at regular intervals throughout the study, to determine whether there are clues to guide us in ensuring that the study sample is rich in the dimension of social withdrawal for both the AD and SZ groups.

3.2. Behavioural tasks

Development of behavioural tasks was primarily the responsibility of P1vital® Products Ltd. and P1vital® Ltd. The behavioural paradigms developed included: FERT (Facial Expression Recognition Task, similar to that described in (Harmer et al., 2013)), DSST (Digit Symbol Substitution Task, similar to digit symbol coding in (Wechsler, 1997)), and EEfRT (Effort Expenditure for Rewards Task (Treadway et al., 2009; Reddy et al., 2015)). Development also included a "scheduler" which delivers tasks at appropriate times / in the appropriate order, and a number of self-report questionnaires. All of this is housed within the online P1vital® 'ePRO' system, and therefore tasks are completed online via a personalised account which researchers create for participants. The ePRO system is built to high, industry-regulation standards, and site staff were all provided with training and materials to provide for standardised data collection procedures across sites. One task, the 'Conners Continuous Performance Task - III', was not possible to develop with ePRO due to licensing issues. This behavioural paradigm was purchased for use in PRISM (MHS® Assessments). A further task, the Hinting Task (Corcoran et al., 1995), is a pen-and-paper dialogue-based task and simply required translation into local languages.

3.3. (f)MRI tasks, sequences, and implementation

The PRISM study involves 4 fMRI data collection sites (3 using Philips Ingenia 3T-scanners and one using a Siemens Prisma 3T-scanner) in two countries (The Netherlands and Spain). Technical variations between scanners are a major source of variability when running multi-centre fMRI studies and can be minimized by careful optimization of procedures and sequence parameters. For PRISM, a task force consisting of consortium members and site technicians identified the best possible scanning parameters through an iterative optimization process. The basic BOLD parameters were standardized between the different scanners, with all major parameters being kept the same and similar advanced shims being performed at all sites. The development of the DTI and ASL sequences involved further customization of available sequences to minimize differences in acquisition parameters whilst maximizing signal-to-noise ratio for each site. Additionally, the procedures for setting-up individual MRI scans during each session (e.g. placing field of view, labelling plane for ASL) were standardized.

Technical differences are easily overshadowed by human and cultural variations, which are more difficult to quantify. To minimize these, the following steps have been taken. All MRI procedures were standardized and researchers were trained and provided with materials to administer these in the same way at all sites. A locked-down computer system and identical peripheral response equipment were provided for task administration. Stimulus sizes were adjusted to occupy the same visual angle in the scanner at all sites, and time-of-day effects were minimized by choosing similar times of day for the assessments, taking into account cultural differences by using slightly later time slots in Spain compared to the Netherlands.

Development of fMRI tasks was the responsibility of P1vital® Products Ltd. and P1vital® Ltd. This comprised the Facial Emotion Processing (FEP) task (similar to that described in (Godlewska et al., 2012)), the Monetary and Social Incentive Delay Task (Rademacher et al., 2010), and a version of the N-back task, up to 2-back (similar to that described in (Smith et al., 2017) but informed by previous studies using this task in AD and MCI populations (Kumar et al., 2017; Migo et al., 2015; McGeown et al., 2008)).

3.4. EEG tasks and implementation

All EEG cognitive paradigms were developed and deployed to sites by Biotrial; for further details see Danjou et al., in this issue. In brief, software development has been performed using an Eprime (v2.010) environment, and operational qualification of the EEG system was conducted through an internal pilot study. EEG setup was replicated on similar hardware and distributed to each study site. Study specific on-site training was delivered by Biotrial staff to site staff and following this a 'dummy' EEG recording was performed by each site and validated by Biotrial prior to EEG accreditation.

3.5. BEHAPP smartphone application

The BEHAPP smartphone application provides a remote, unobtrusive and objective measure of sociability and social exploration in a longitudinal daily-life manner (Eskes et al., 2016; www.behapp.org). BEHAPP passively monitors smartphone activities, including frequency, duration and diversity of events, such as incoming and outgoing phone calls (with number encryption), SMS usage, and social media activities (e.g., WhatsApp and Facebook events). It is important to note that no content (e.g., from calls or messages) is being collected. In addition, GPS and Wi-Fi-access points are being sampled in order to, for example, integrate movement patterns with social density measures. While both social and non-social measures are being monitored by using these measures, it is aimed to provide an objective and quantitative measure of social withdrawal using BeHapp data features as part of the PRISM project. Data is secured using industry standard security measures (see also van der Wee et al., in this issue).

Installing and providing data through BEHAPP is optional in this study. Participants who are willing to contribute BEHAPP data, but who do not have an Android smartphone, are offered a research phone for the duration of the study.

3.6. Case Report Form (CRF) and electronic Case Report Form (eCRF)

The PRISM Case Report Form (CRF) captures demographic and clinical data as well as other information about the details of the assessment days from individual participants. Data is entered into an electronic Case Report Form (eCRF), supported by commercial OpenClinica software, to support comprehensive, efficient, and high-quality data capture, and to allow for more effective cross-site data monitoring and management. All relevant site staff are provided with standardised training on the PRISM CRF and eCRF.

4. Data analysis

All data, including MRI and EEG data, will undergo quality checks to ensure the highest possible data quality. Participant-level endpoints will then be extracted for MRI (e.g. average brain activity within pre-defined ROIs and contrasts of interest specified in each fMRI task; fractional anisotropy from DTI; fractional perfusion from ASL), EEG (e.g. latency, amplitude, and spectral components of event-related potentials), and behavioural data.

More traditional, group-based analyses will be completed on this endpoint data, for example comparing the different participant groups using a 3-way ANOVA design of AD, SZ, and HCs. Study site will be included as a covariate of no interest, and analyses will also include covariates for age, gender, and social withdrawal indices. Medication information will not be entered as a standard covariate (due to expected variability in type), but will be used in post-hoc sensitivity analyses where the influence of medication can be checked. This will allow analysis of patient classification (e.g. SZ vs. AD, or patient groups vs. HCs) whilst also allowing an exploration of the effects of aging and medication. This approach will also allow investigation of the influence of social withdrawal dimensions (e.g. through WHODAS score, loneliness ratings, or sociability information from the BEHAPP app) across the participant groups.

However, these traditional methods are limited in the extent to which they can serve the goals of PRISM, which is to explore whether there is a *set* of quantifiable biological parameters that can cluster and differentiate SZ and AD patients, possibly related to the neural or biological substrates of social withdrawal. This ambitious goal is better served by novel statistical methods aimed at clustering data.

5. Cluster analysis

Group-level analyses implement comparisons that are based on researcher-defined participant labels. There is growing consensus that these labels are not fine-grained enough to allow proper investigation of the heterogeneity typically observed in patient groups. Therefore, analyses aimed at clustering unlabelled datasets will be performed, with the aim of obtaining data-driven groups of patients that share a common feature or set of features (fMRI, EEG, behavioural). These analyses are based on the hypothesis that multiple underlying neurobiological causes can lead to similar behavioural profiles, and conversely, that various behavioural profiles can be the result of similar underlying neurobiology.

Inputs for the clustering analyses will be the primary endpoints from the MRI, EEG, and behavioural analyses. For fMRI specifically, both ROI-based endpoints and whole-brain data will be used. Medication can be used to characterise the retrieved subject groupings. In the clustering analysis, feature selection techniques will pick out those covariates that best explain the most relevant clinical symptoms or symptom constellations, and will reveal and rank potential predictive and prognostic biomarkers. A normative modelling approach will be employed, that focuses on accurately modelling variation in biological measures across the entire study cohort. This is done using Gaussian process regression (GPR) to predict a set of biological response variables (e.g. neuroimaging data) from a set of clinically relevant covariates (e.g. trait scores) while providing estimates of predictive confidence for every prediction. In a second step we use the distribution learned from the normative modelling approach (using healthy control data collected from this and prior studies) to make predictions for individual participants to provide a score quantifying how much each individual subject deviates from the normative model ('Normative probability mapping'). Thereby we will be able to uncover the underlying biophysical mechanisms, guided by machine learning, and to define the most relevant quantitative systems measures that can be used for the identification of underlying mechanisms of pathophysiology.

6. Summary

This study will use validated neuroimaging, neuropsychological, and neurophysiological assessments as well as epigenetics to explore social withdrawal and cognitive deficits in AD and SZ. Healthy control data will allow exploration of how biomarkers identified in the patient groups compare with normative data, and whether there is independence of identified biomarkers from the effects of normal aging. Clustering analysis will aim to reveal data-driven groups of patients that share a common feature or set of features (fMRI, EEG, behavioural, and/or self-report). Findings will contribute to the understanding of common pathophysiological mechanisms that drive symptoms such as

social withdrawal, potentially revealing novel targets for treatment of disorders including SZ and AD.

Study Status

Recruitment started in August 2017.

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Conflict of Interests

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